REMARKS

It is respectfully requested that the above amendment be entered pursuant to the provisions of 37 C.F.R. §1.116(b); that this application be reconsidered in view of the above amendment and the following remarks; and that all of the claims remaining in this application be allowed.

Amendments to claims

Applicants have requested that claim 19 be amended to clarify that the claimed invention is directed to the treatment and prevention of T-cell-mediated or inflammatory disorders, including contact hypersensitivity, psoriasis, rheumatoid arthritis, scleroderma, lupus, diabetes mellitus, organ rejection, miscarriage, multiple sclerosis, inflammatory bowel disease, and graft versus host disease.

Applicants have requested deletion of the term "atherosclerosis" from claim 19. Insofar as this amendment reduces claim scope without presenting any new claim language, no new issues are raised by the amendment.

Applicants have also requested addition of the term "contact hypersensitivity" to the list of diseases recited in the Markush group of claim 19. In view of the fact that the Office Action of November 19, 2002 at page 3 has already stated that the Specification is enabling for the disease of contact hypersensitivity, Applicants submit that the addition of this claim term will raise no new issues with respect to patentability.

Applicants submit that these amendments places the claim in better condition for allowance or, alternatively, simplifies issues for Appeal and, accordingly, entry of the amendments is therefore proper under 37 C.F.R. §1.116(b). Therefore, entry of this amendment is earnestly solicited. Applicants reserve the right to pursue the canceled subject matter in a continuation or divisional case.

Applicants also request cancellation of claims 31-45, without prejudice or disclaimer, in compliance with the Restriction Requirement issued in the Office Action of November 19, 2002.

These amendments have been made in accordance with 37 C.F.R. §1.121 as amended on November 7, 2000. As required, attached hereto in Appendix A is an illustration of the changes made to Claim 19.

Conformed Copy of the Pending Claims

Claims 19-30 are pending in this case. To facilitate review, attached hereto as Appendix B is a conformed copy of the pending claims wherein the amendments requested to claim 19 have been presumed to have been entered.

Restriction Requirement

The Office Action of November 19, 2002 constructively elected for prosecution pending claims 19-30. Claims 31-45 were withdrawn from consideration as being drawn to a non-elected invention.

Applicants acknowledge the constructive election of claims 19-30 and herein cancel, without prejudice or disclaimer, claims 31-45, drawn to non-elected inventions. Applicants reserve the right to prosecute the subject matter of claims 31-45 in a future application claiming priority to the instant application.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-18 (now canceled and replaced with claims 19-30) remain rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out that which Applicants regards as their invention. Specifically, claims 19-30 are rejected because (i) claim 19 does not recite "CHS," a T-cell-mediated or inflammatory disorder described in the specification and allegedly relating to a preferred embodiment of the invention, and (ii) because at least three of the diseases recited in claim 19 are also recited as endothelial dysfunction disorder in co-pending U.S. Application Serial No. 09/866,569 (herein, "the '569 application"). Office Action of November 19, 2002 at page 3.

With regard to the first issue, Applicants submit that the decision not to recite CHS among the list of diseases in claim 19 should not raise a rejection for indefiniteness. Diseases for which the instant invention is useful for treating are disclosed in the Specification, for example, at page 5, lines 15-24 and page 12, lines 14-23. Note that CHS is only one of the diseases recited in the Specification. While Examples 1 and 2 are drawn to treatment of CHS, the Specification clearly indicates that the Examples are for illustrative purposes only (page 12, lines 24-25).

Nonetheless, in the interest of compact prosecution, Applicants have requested that claim 19 be amended to include the recitation of CHS. Support for this amendment is found throughout the Specification, including but not limited to, page 5, line 21; Examples 1 and 2 at pages 13-16; and page 16 at lines 3-16.

With regard to the second issue, related to the double patenting rejection (also discussed below), Applicants submit that the above requested Amendment to claim 19, deleting the recitation of "atherosclerosis," obviates the rejection in view of the now pending claims in the co-pending '569 application. Instant claim 19 now recites disorders "selected from the group consisting of contact hypersensitivity, psoriasis, rheumatoid arthritis, scleroderma, lupus, diabetes mellitus, organ rejection, miscarriage, multiple sclerosis, inflammatory bowel disease, and graft versus host disease." None of these diseases are now recited in the claims (particularly claim 16) of the co-pending '569 application. For the Examiner's convenience, a copy of the most recent Amendment and Reply to Official Action in co-pending U.S. Application Serial No. 09/866,569, is enclosed herewith as Exhibit A.

For at least the reasons above, Applicants submit that the rejection of claim 19 under 35 U.S.C. § 112, second paragraph, is no longer appropriate and request withdrawal of the rejection.

Enablement rejection under 35 U.S.C. § 112, first paragraph

Claims 19-30 are rejected under 35 U.S.C. § 112, first paragraph, because the Specification "while being enabling for [a] method of treating CHS, does not reasonably provide enablement for any other diseases listed in claim 19." Office Action of November 19, 2002 at page 3. Specifically, the Office Action alleges that treatment of T-cell-mediated or inflammatory disorders such as rheumatoid arthritis and multiple sclerosis are not trivial matters and/or are notoriously difficult to treat. Applicants submit that the instant rejection is without legal or factual justification.

An assertion by the Patent Office that a disclosure is not enabling for the full scope of the claims "must be supported by evidence or reasoning substantiating the doubts so expressed." *In re Dinh-Nguyen and Stenhagen*, 181 USPQ 46, 47 (CCPA. 1974). In this case, the Office Action of November 19, 2002 has failed to provide evidence that the

Specification would not enable one skilled in the art to make and use the invention. Morever, the Office Action appears to indicate that a drug must be proven successful for a claimed method of treatment to qualify for patent protection. Yet patent law in the United States does not require that such proof, which is tantamount to FDA approval, is a prerequisite for obtaining patent protect on a drug. Indeed if FDA approval were a prerequisite for patent protection under the enablement requirement of 35 U.S.C. § 112, first paragraph, few pharmaceutical patents would ever issue in the United States. For at least this reason, there is no basis for maintaining the enablement rejection.

Neither is the above enablement rejection supported factually, in view of the scientific literature. As described in the Specification (page 16, lines 3-16) the administration of apoptotic bodies up-regulates Th-2-derived cytokines (*e.g.*, IL-10) and down-regulates inflammatory cytokines such as TNFγ, IL-6, and IL-12. The Specification states that these cytokines are implicated in the diseases presently recited in claim 19, *i.e.*, contact hypersensitivity, psoriasis, rheumatoid arthritis, scleroderma, lupus, diabetes mellitus, organ rejection, miscarriage, multiple sclerosis, inflammatory bowel disease, and graft versus host disease (page 16, lines 3-16). Moreover, as discussed below, a survey of recent immunology textbooks supports Applicants' assertions, and provides evidence that Applicants' invention, as set forth in the specification, is enabling for the full scope of the claims.

Th-1 cells are involved in cell-mediated inflammatory responses and secrete IL-2, TNF, and IFN. Th-2 cells participate in humoral and allergic immune responses and secrete IL-4, IL-5, IL-6, IL-8, IL-10, and IL-13. Lahita, R.G. *ed.* (2000) *Textbook of the Autoimmune Diseases*, Lippincott Williams & Wilkins, Philadelphia, Chapter 9, p. 101 (a photocopy of Chapter 9 is enclosed as Exhibit B). IL-6 induces growth and differentiation in T and B-cells and IL-12 strongly stimulates T-cell differentiation to Th-1 cells as well as well as activation of natural killer cells. *Id.* at 103, 105. TNF regulates cytokine production and is well-known to play a role in cell-mediated immune response. *Id.* at 101, 104. In contrast IL-10 is known to (i) inhibit antigen presentation, (ii) inhibit pro-inflammatory cytokine production by macrophages, (iii) suppress Th-1-dependent immune response, and (iv) enhance and/or support Th-2-mediated immune response. *Id.* at 103, 105; Fathman, C.G. *ed.* (2000) Interleukin-10: therapeutic prospects in rheumatoid

arthritis, *in Current Directions in Autoimmunity*, Karger Pub. Basel, Switzerland, p. 126 (a photocopy of the relevant article is enclosed as Exhibit C).

The roles of many of these cytokines have been investigated with respect to autoimmune diseases. For example, TNF is known to be important in rheumatoid arthritis because it induces the release of matrix metalloproteinases from neutrophils, chondrocytes, and fibroblqasts and induces the expression of leukocyte endothelial adhesion molecules, leading to leukocyte migration and inflammation in affected tissues. Lahita at 107. TNF also induces the production of pro-inflammatory cytokines including IL-6. *Id.* at 108. Both IL-6 and IL-12 are closely associated with establishing and/or maintaining a preponderance of Th-1 cells at sites of inflammation in rheumatoid arthritis. *Id.* Evidence obtained from animal models of rheumatoid arthritis also implicates IL-10 in the disease. For example, IL-10 treatment suppresses disease symptoms while treatment with anti-IL-10 antibodies increases disease severity. Fathman at 137.

IL-10 administration, whether through administration of the purified protein or using gene therapy-based approaches, has been the subject of considerable research and ongoing clinical studies with respect to the treatment of rheumatoid arthritis. *Id.* at 134-141. In fact, the Arthritis Foundation (Atlanta, Georgia) specifically recognized IL-10 administration as a potential future treatment for arthritis. Klippel, J.H. *ed.* (2001) *Primer on the Rheumatic Diseases*, 12th Edition, Arthritis Foundation, Atlanta, Georgia, p. 64 (a photocopy of relevant sections is enclosed as Exhibit D).

Scientific and clinical evidence also suggest that diabetes mellitus is a Th-1 mediated disease resulting from dysregulation of the normal Th-2:Th-1 ratio. Lahita at 111. Restoring or artificially elevating the Th-2:Th-1 ratio has been recognized as a potential therapy for diabetes mellitus. *Id.* at 111-112. Consistent with these predictions, it has been reported that systemic administration of IL-10 to nonobese mice prevents the onset of diabetes. Fathman at 136.

Pro-inflammatory Th-1-derived cytokines such as TNF and IL-12 are also known to be involved in inflammatory bowel disease, while IL-10 is known to be immunosuppressive. Lahita at Chapter 15, page 245 (a photocopy of Chapter 15 is enclosed as Exhibit E). For example, administration of IL-10 reduces cell-mediated

immune response to gut antigens while deletion of the IL-10 gene leads to chronic inflammatory bowel disease-like symptoms in transgenic mice. *Id.* at 245, 260.

While Applicants have not exhaustively detailed cytokine profiles for each and every disease recited in claim 19, it should be appreciated from the above review of recent immunological texts that there is a significant body of scientific and clinical evidence drawn to the mechanisms of many autoimmune diseases. Moreover, much of this information is so widely and generally accepted that it is found in modern immunology textbooks, such as those cited above. Applicants have not resorted to obscure journal references to support the teachings of the instant Specification.

The Office Action of November 19, 2002 states that T-cell-mediated or inflammatory disorders such as rheumatoid arthritis and multiple sclerosis are notoriously difficult to treat. Indeed, these are diseases for which satisfactory treatments have yet to be developed. However, the immune dysfunctions that result in these diseases are not entirely unknown and, in some cases, the molecular genetic characteristics of such autoimmune diseases are quite well characterized. In particular, both rheumatoid arthritis and multiple sclerosis show typical Th-1 cytokine profiles. Lahita at 111 and *supra*. Accordingly, there is no reason that one skilled in the art would doubt, *a priori*, that the invention could not be used to treat rheumatoid arthritis, multiple sclerosis, or the other diseases listed in claim 19.

It is well-settled patent law that the test of enablement is whether one skilled in the relevant art could make and use the invention without undue experimentation. *In re Wands*, 858 F.2d. 731, 737 (Fed Cir. 1988). The Office Action of November 19, 2002 at page 4 suggests that

> [i]t might take years through lengthy clinical trials for research clinicians to determine (1) which source of the cells to make apoptotic cells and/or apoptotic bodies for each of specific diseases, (2) a specific dose for any one of the diseases listed in the instant claims.

Yet these issues, which presumably relate to the amount of experimentation necessary to make and practice the invention, are straightforward in view of the Specification.

The source of the apoptotic cells and/or bodies is, for example, the mammalian patient or an individual immunologically compatible with the mammalian patient. Specification at, for example, page 7, lines 12-24. In this respect, the processes of making and using the disclosed invention is not substantially different depending on whether the disease is contact

hypersensitivity, rheumatoid arthritis, or inflammatory bowel disease. The practitioner need only know that the disease to be treated has the hallmarks of autoimmune diseases as set forth in the Specification, for example, at page 16, lines 3-16.

In addition, there is no reason to believe that the level of treatment (*e.g.*, the amount of stress exerted in preparing the apoptotic cells and/or bodies) or the number of viable cells used in the treatment, which together comprise the treatment "dose," will be more difficult to establish for any one of the diseases in claim 19 compared to CHS. These treatment parameters are discussed at, for example, page 9, lines 14-19; page 10, lines 15-27; page 11, lines 1-7; and page 11, line 22 - page 12, line 2 of the Specification.

One skilled in the art will recognize that initial dosage determination (and even continuing dosage adjustment) is a necessary part of many well-established and widely-used drug regimens, *e.g.*, hormone replacement therapy, treatment of psychological disorders, etc. To maintain that any invention requiring experimentation to determine correct dosage is not fully enabled would automatically render vast numbers of issued drug patents potentially invalid. Thus, in view of the fact that some amount dosage determination is accepted in the field of experimental medicine, Applicants submit that the instant invention would not require undue experimentation for use in the treatment of CHS or the other diseases recited in claim 19.

Accordingly, the Office Action of November 19, 2002 has failed to state the reasons why a practitioner would not know how to make or use the invention for treatment of the diseases recited in claim 19 and has failed to set forth a *prima facie* case for lack of enablement for Applicants to rebut.

For at least the above reasons, Applicants submit that the instant patent application is fully enabling for subject matter within the full scope of the claims. Accordingly, Applicants respectfully request withdrawal of the outstanding enablement rejection under 35 U.S.C. § 112, first paragraph.

Provisional Type Double Patenting Rejection

Claims 19 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 11 (now canceled and replaced with claim 16) of the co-pending '569 application. Specifically, the Office Action

of February 22, 2002 at page 6 states that "both claims are drawn in part to treatment of inflammatory bowel disease, atherosclerosis, and graft versus host disease with apoptotic bodies and/or cells." This rejection is traversed for the following reasons.

Applicants first note that an obviousness-type double patenting rejection is analogous to an obviousness rejection under 35 U.S.C. §103(a) except that application underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obvious-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. §103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991). If such an assumption is in error, the undersigned would appreciate clarification from the Office.

The instant obviousness-type double patenting rejection provides no reference(s) to combine with the teachings of the instant patent application to make obvious the claims in the co-pending '569 application.[1] It is therefore unclear why one skilled in the art would consider the claims of the instant application obvious in view of the claims of the '569 application. Accordingly, Applicants submit that the obvious-type double patenting rejection is in error because it fails to provide for a *prima facie* case of obviousness against the claimed invention. At least for these reasons, the obvious-type double patenting rejection should be withdrawn.

Nonetheless, in the interest of compact prosecution, Applicants have amended instant claim 19 to delete the recitation of "atherosclerosis." In view of this amendment, and the claim amendment in the co-pending '569 application (a copy of the most recent Amendment and Reply to Official Action in co-pending U.S. Application Serial No. 09/866,569, is enclosed herewith as Exhibit A), none of the diseases recited in claim 19 of the instant application are recited in the claims of the '569 application. Applicant's submit that there is no longer any basis for the obvious-type double patenting rejection, and respectfully request that it should be withdrawn.

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[1] Applicants note that claims 17-27 of the co-pending '569 application were rejected over claims 3-14 (now canceled) of the instant application in view of Henry, *et al.*(1999) Pathobio. 67:306-310 and Dini, *et al.*(1995) J. Cell. Sci., 108:967-97. However, no such references are provided in support of the instant obvious-type double-patenting rejection.

Co-pending Application/Publication

Applicants wish to bring the Examiner's attention to co-pending and allowed application 09/760,600, which is commonly assigned.

Applicants also wish to bring the Examiner's attention to PCT Publication No. WO 01/66785, published September 13, 2001.

US PAT 6512895

CONCLUSION

In view of the above, Applicants submit that this application is in condition for allowance. Early notice to that effect is earnestly solicited.

Respectfully submitted,

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APPENDIX A

MARKED UP VERSION OF CLAIM 19 SHOWING CHANGES MADE

Applicants have requested the following amendment to claim 19:

19. A method for treatment and/or prophylaxis in mammalian patients with T-cell-mediated or inflammatory disorders, wherein the disorder is selected from the group consisting of contact hypersensitivity, psoriasis, rheumatoid arthritis, scleroderma, lupus, diabetes mellitus, organ rejection, miscarriage, multiple sclerosis, inflammatory bowel disease, [atherosclerosis,] and graft versus host disease, which method comprises administering to the patient an effective amount of apoptotic bodies.

APPENDIX B

CONFORMED COPY OF PENDING CLAIMS WITH AMENDMENT TO CLAIM 19 ENTERED

19. A method for treatment and/or prophylaxis in mammalian patients with T-cell-mediated or inflammatory disorders, wherein the disorder is selected from the group consisting of contact hypersensitivity, psoriasis, rheumatoid arthritis, scleroderma, lupus, diabetes mellitus, organ rejection, miscarriage, multiple sclerosis, inflammatory bowel disease, and graft versus host disease, which method comprises administering to the patient an effective amount of apoptotic bodies.

20. The method of claim 19, wherein the apoptotic bodies are in a liquid suspension along with viable cells.

21. The method of claim 20, wherein the apoptotic bodies comprise from 10% to 90% of the cellular portion of the suspension.

22. The method of claim 21, wherein the apoptotic bodies comprise from 30% to 70% of the cellular portion of the suspension.

23. The method of claim 19, wherein the apoptotic bodies are derived from extracorporeal treatment of blood cells compatible with those of the mammalian patient.

24. The method of claim 19, wherein the apoptotic bodies are derived from established cultured cell lines.

25. The method of claim 23, wherein the blood cells are white blood cells of blood compatible with that of the mammalian patient.

26. The method of claim 25, wherein the blood cells are the patient's own white blood cells.

27. The method of claim 26, wherein the blood cells are the patient's own T lymphocytes.

28. The method of claim 19, further comprising administering to a human patient a dosage of apoptotic bodies comprising from 10,000 to 10,000,000 apoptotic bodies per kilogram body weight of the patient.

29. The method of claim 28, wherein the dosage contains from 500,000 to 5,000,000 apoptotic bodies per kilogram body weight of the patient.

30. The method of claim 28, wherein the dosage contains from 1,500,000 to 4,000,000 apoptotic bodies per kilogram body weight of the patient.